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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,724	10/18/2006	**Matthew Graeme Dunckley**	87792.026005	8410

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ZARA, JANE J	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,724	DUNCKLEY ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9-29-08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,26,28,30-38,40-43 and 61-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,26,28,30-38,40-43 and 61-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 9-29-08.

Claims 23, 26, 28, 30-38, 40-43, 61-70 are pending in the instant application.

Election/Restrictions

Applicant's election with traverse of Group III, claims 30, 31, 33-37, SMN2 as the first binding domain, and SF2/ASF as the RNA splicing factor, and treating spinal muscular atrophy (SMA), in the reply filed on 9-29-08 is acknowledged. The traversal is on the ground(s) that all of the different methods involve the use of a nucleic acid molecule of claim 23, and all relate to enhancing splicing. This is not found fully persuasive because the different and distinct target binding sites are each chemically and structurally distinct and the searches involved are not coextensive, although they may be overlapping. In addition, the methods utilize distinct steps which are not used in the others' methods, require the administration of different and distinct molecules, and require the measurement of different biological, biochemical or clinical outcomes that are not required in each others' methods (*see, e.g.,* methods of treating conditions involving defective RNA splicing in a subject, methods of treating conditions involving defective translation in a subject, methods of enhancing polyadenylation, methods of affecting RNA processing, methods of designing nucleic acid molecules). To the extent that claims are drawn to the same active steps,

including the administration of a patentably distinct composition, these claims have been rejoined and examined on their merits as set forth below.

The requirement is still deemed proper and is therefore made FINAL.

Claim 43, as it pertains to diseases other than spinal muscular atrophy, is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9-29-08.

Information Disclosure Statement

The information disclosure statement filed 12-30-05 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the citations for the articles do not contain titles, as required by 37 CFR 1.98(b). It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 26, 28, 30-38, 40-43, 61-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods of recruiting RNA splicing factors, enhancing exonic incorporation, and recruiting any splicing factor to any target RNA species for treating any condition characterized by defective RNA splicing in an individual, comprising the administration of a nucleic acid molecule comprising a first domain which forms a specific binding pair with a target sequence which is within 100 nucleotides of a defective RNA splicing site on a target RNA, and which nucleic acid molecule further comprises a second specific binding pair with an RNA splicing factor which is optionally a UsnRNP, and which second domain is optionally complementary or non-complementary to the second target RNA species (or which is optionally SEQ ID NO. 16 or 5' CAGGUAAGU 3').

The specification, claims and the art do not adequately describe the distinguishing features or attributes concisely shared by the members of the genus of compounds claimed, and which provide for the functions claimed, which

functions include enhancing exonic incorporation, and recruiting any splicing factor to any target RNA species for treating any condition characterized by defective RNA splicing in an individual.

The specification teaches the characterization of a series of oligonucleotides with tails for recruiting hTRA2β and SF2/ASF, whereby a specific increase in the proportion of exon 7 inclusion in SMN2 mRNA was observed in vitro when using 5'GAA but not with 5'GGA. *See, e.g.,* page 65 of the instant disclosure, teaching that hTra2-B1 is thought to be rendered inaccessible to 5'GGA due to possible secondary structural constraints. See also page 66, showing that the addition of hTra2B to the nuclear extract stimulates inclusion in SMN1, but has relatively little effect on SMN2 in the presence of either 5'GGA or 5'GAA, suggesting that other factors limit improvements in corrective efficiency that appear unpredictable.

The specification fails to teach successful in vitro and in vivo splicing corrections using a representative number of species of the broadly claimed genus, which encompasses a first domain which forms a specific binding pair with any target sequence which is within 100 nucleotides of any defective RNA splicing site on a target RNA, and which nucleic acid molecule further comprises a second specific binding pair with any RNA splicing factor which is optionally a UsnRNP, and which second domain is optionally complementary or non-complementary to any second target RNA species. The specification also fails to teach a representative number of species of nucleic acids providing therapeutic

effects for any disease or condition characterized by defective or undesirable RNA splicing in an individual.

The examples provided at the time of filing, therefore, are not representative or correlative of the expansive genus of compounds claimed. Concise structural features that could distinguish structures within the genus from others are missing from the disclosure. (*e.g.*, What oligonucleotide or nucleic acid sequences have been found to provide for the effects, functions or treatments claimed?). No common structural attributes identify the members of the broadly claimed genus, and distinguish members within the claimed genus from those outside of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus claimed.

Thus, Applicant was not in possession of the broadly claimed genus.

Claims 23, 26, 28, 30-38, 40-43, 61-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro increase in splicing efficiency by enhanced inclusion of exon 7 within SMN2 using particularly described 5'GGA and 5'GAA containing antisense oligonucleotides of SEQ ID NOs. 8 and 10, does not reasonably provide enablement for methods of recruiting RNA splicing factors, enhancing exonic incorporation, and recruiting any splicing factor to any target RNA species for treating any condition characterized by defective RNA splicing in an individual,

comprising the administration of a representative number of species of the broad genus of compounds claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of recruiting RNA splicing factors, enhancing exonic incorporation, and recruiting any splicing factor to any target RNA species for treating any condition characterized by defective RNA splicing in an individual, comprising the administration of a nucleic acid molecule comprising a first domain which forms a specific binding pair with a target sequence which is within 100 nucleotides of a defective RNA splicing site on a target RNA, and which nucleic acid molecule further comprises a second specific binding pair with an RNA splicing factor which is optionally a UsnRNP, and which second domain is optionally complementary or non-complementary to the second target RNA species (or which is optionally SEQ ID NO. 16 or 5' CAGGUAAGU 3').

The state of the prior art and the predictability or unpredictability of the art. Branch and Crooke teach that the in vivo (whole organism) application of molecules is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target molecules. (See entire text of A. Branch, Trends in Biochem. Sci., 23, 45-50, 1998; and S. Crooke, Ann. Rev. Med., Vol. 55, pages 61-95, 2004, esp. pages 71-72, 74, 81, 84-85).

Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and

of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release... remains one of the major hurdles in the field." (See Peracchi et al, Rev. Med. Virol., 14, pages 47-64, 2004, abstract on page 47 and text on page 51).

Cellular uptake by appropriate target cells is a rate limiting step that has yet to be overcome in achieving predictable clinical efficacy. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of small molecules in vitro and in vivo (see Agrawal et al, Molecular Med. Today, Vol. 6, pages 72-81, 2000, especially at pages 79-80; see Chirila et al, Biomaterials, Vol. 23, pages 321-342, 2002, especially pages 326-327 for a general review of the important and inordinately difficult challenges of the delivery of therapeutic molecules to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. The specification teaches the characterization of a series of oligonucleotides with tails for recruiting hTRA2β and SF2/ASF, whereby a specific increase in the proportion of exon 7 inclusion in SMN2 mRNA was observed in vitro when using 5'GAA but not with 5'GGA. The specification also teaches the in vitro increase in splicing efficiency by enhanced inclusion of exon 7 within SMN2 using particularly described 5'GGA and 5'GAA containing antisense oligonucleotides of SEQ ID NOs. 8 and 10

The specification fails to teach successful in vitro and in vivo splicing corrections using a representative number of species of the broadly claimed genus, which encompasses a first domain which forms a specific binding pair with any target sequence which is within 100 nucleotides of any defective RNA splicing site on a target RNA, and which nucleic acid molecule further comprises a second specific binding pair with any RNA splicing factor which is optionally a UsnRNP, and which second domain is optionally complementary or non-complementary to any second target RNA species. The specification also fails to teach a representative number of species of nucleic acids providing therapeutic effects for any disease or condition characterized by defective or undesirable RNA splicing in an individual. *See, e.g.,* page 65 of the instant disclosure, teaching that hTra2-B1 is thought to be rendered inaccessible to 5'GGA due to possible secondary structural constraints. See also page 66, showing that the addition of hTra2B to the nuclear extract stimulates inclusion in SMN1, but has relatively little effect on SMN2 in the presence of either 5'GGA or 5'GAA, suggesting that other factors limit improvements in corrective efficiency that appear unpredictable.

The examples provided at the time of filing, therefore, are not representative or correlative of the ability to enhance exonic incorporation, and recruit any splicing factor to any target RNA species for treating any condition characterized by defective RNA splicing in an individual, comprising the administration of a representative number of species of the broad genus of compounds claimed, encompassing nucleic acid molecules comprising a first domain which forms a

specific binding pair with any target sequence which is within 100 nucleotides of any defective RNA splicing site on a target RNA, and which nucleic acid molecule further comprises a second specific binding pair with an RNA splicing factor which is optionally a UsnRNP, and which second domain is optionally complementary or non-complementary to the second target RNA.

Applicants have not provided adequate guidance in the specification toward treating any condition associated with defective or undesirable RNA splicing in an individual. One skilled in the art would not accept on its face the examples given in the specification of the in vitro enhancement of exon 7 inclusion using the antisense sequences claimed as being correlative or representative of the ability to recruit RNA splicing factors, enhance any exonic incorporation, and recruit any splicing factor to any target RNA species for treating any condition characterized by defective RNA splicing in an individual, comprising the administration of a representative number of species of compounds claimed. There is a lack of guidance in the specification and an unpredictability associated with the successful targeting and delivery of therapeutic oligonucleotides to appropriate target cells in an organism.

The breadth of the claims and the quantity of experimentation required. The claims are drawn to methods of recruiting RNA splicing factors, enhancing exonic incorporation, and recruiting any splicing factor to any target RNA species for treating any condition characterized by defective RNA splicing in an individual, comprising the administration of a nucleic acid molecule comprising a first domain which forms a specific binding pair with a target sequence which is

within 100 nucleotides of a defective RNA splicing site on a target RNA, and which nucleic acid molecule further comprises a second specific binding pair with an RNA splicing factor which is optionally a UsnRNP, and which second domain is optionally complementary or non-complementary to the second target RNA species (or which is optionally SEQ ID NO. 16 or 5' CAGGUAAGU 3').

The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of a representative number of compounds claimed, whereby exonic incorporation has been enhanced, and recruitment has occurred for any splicing factor to any target RNA species for treating any condition characterized by defective RNA splicing in an individual. Other experimentation required to practice the invention claimed includes determining accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues in an organism, whereby the compound or compounds are effectively delivered in adequate quantities to the target cells. Since the specification fails to provide sufficient guidance for the methods using the therapeutic compositions claimed, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 23, 26, 28, 30-38, 40-42, 61-65 are rejected under 35 U.S.C. 102(e) as being anticipated by Mitchell et al (US 2003/0077754).

Mitchell et al (US 2003/0077754) teach methods of recruiting RNA splicing factors, enhancing exonic incorporation, and recruiting a splicing factor to a target RNA species for treating a condition characterized by defective RNA splicing in an individual, comprising the administration of a nucleic acid molecule comprising a first domain which forms a specific binding pair with a target sequence which is within 100 nucleotides of a defective RNA splicing site on a target RNA, and which nucleic acid molecule further comprises a second specific binding pair with an RNA splicing factor which is optionally a UsnRNP, and which

second domain is optionally complementary or non-complementary to the second target RNA species (see the abstract, pages 2-3, figures 1, 2, 3, 6, 8, 9, 20, 21, 23, 24, 37, 40, 41, pages 5-6, 8-9, 14-15; example 8, page 18; example 9, page 19; example 11, pages 22-23; claims 1, 2, 7-11, 16-19, 21-23, 26, 27, 32-36, 42-45, 48, 49).

Claims 23, 26, 28, 30-38, 40-42, 61-65, and 69 are rejected under 35 U.S.C. 102(e) as being anticipated by Mitchell et al (US 2004/0126774).

Mitchell et al (US 2004/0126774) teach methods of recruiting RNA splicing factors, enhancing exonic incorporation, and recruiting a splicing factor to a target RNA species, comprising the administration of a nucleic acid molecule comprising a first domain which forms a specific binding pair with a target sequence which is within 100 nucleotides of a defective RNA splicing site on a target RNA, and which nucleic acid molecule further comprises a second specific binding pair with an RNA splicing factor which is optionally a UsnRNP, and which second domain is optionally complementary or non-complementary to the second target RNA species, and optionally comprises CAGGUAAGU (see the abstract; pages 1-6, esp. paragraphs 0008----9, 0013, 0015, 0016, 0019-0020, 0037, 0039, 0040, 0042-0044, 0047-0051, 0062, 0065, claims 1-11, 16-36).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23, 26, 28, 30-38, 40-43, 61- 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Mitchell et al (US 2003/0077754) and Mitchell et al (US 2004/0126774) as applied to claims 23, 26, 28, 30-38, 40-42, 61-65, and 69 above, and further in view of Lim et al (J. Biol. Chem., Vol. 276, No. 48, pages 45,476-45,483, 2001, see IDS document No. 61, filed 12-30-05), and Lorson et al (Proc. Natl. Acad. Sci., Vol. 96, pages 6307-6311, 1999, see IDS document No. 64, filed 12-30-05), the combination further in view of Dunckley et al (Human Molec. Genetics, Vol. 5, No. 1, pages 1083-1090, 1995, see IDS document No. 32, filed 12-30-05) insofar as the claims are drawn to methods of recruiting RNA splicing factors, enhancing exonic incorporation, and recruiting a splicing factor to a target RNA species in vitro for testing candidate compounds for their treatment of a condition characterized by defective RNA splicing in an individual.

Mitchell et al (US 2003/0077754) teach methods of recruiting RNA splicing factors, enhancing exonic incorporation, and recruiting a splicing factor to a target RNA species for treating a condition characterized by defective RNA splicing in an individual, comprising the administration of a nucleic acid molecule comprising a first domain which forms a specific binding pair with a target sequence which is within 100 nucleotides of a defective RNA splicing site on a target RNA, and which nucleic acid molecule further comprises a second specific

binding pair with an RNA splicing factor which is optionally a UsnRNP, and which second domain is optionally complementary or non-complementary to the second target RNA species (see the abstract, pages 2-3, figures 1, 2, 3, 6, 8, 9, 20, 21, 23, 24, 37, 40, 41, pages 5-6, 8-9, 14-15; example 8, page 18; example 9, page 19; example 11, pages 22-23; claims 1, 2, 7-11, 16-19, 21-23, 26, 27, 32-36, 42-45, 48, 49).

Mitchell et al (US 2004/0126774) teach methods of recruiting RNA splicing factors, enhancing exonic incorporation, and recruiting a splicing factor to a target RNA species, comprising the administration of a nucleic acid molecule comprising a first domain which forms a specific binding pair with a target sequence which is within 100 nucleotides of a defective RNA splicing site on a target RNA, and which nucleic acid molecule further comprises a second specific binding pair with an RNA splicing factor which is optionally a UsnRNP, and which second domain is optionally complementary or non-complementary to the second target RNA species, and optionally comprises CAGGUAAGU (see the abstract; pages 1-6, esp. paragraphs 0008----9, 0013, 0015, 0016, 0019-0020, 0037, 0039, 0040, 0042-0044, 0047-0051, 0062, 0065, claims 1-11, 16-36).

The primary references of Mitchell and Mitchell do not teach the mutation or mutations affecting the correct splicing of SMN genes and the involvement of this mutation in spinal muscular atrophy, nor the incorporation of 2'-O-methyl or phosphorothioate internucleotide modifications into oligonucleotides.

Lorson et al (Proc. Natl. Acad. Sci., Vol. 96, pages 6307-6311, 1999, see IDS document No. 64, filed 12-30-05) teach the single nucleotide mutation in the splice site of the SMN gene which regulates splicing and teaches a direct relationship between this single nucleotide mutation, the presence of disease and exon 7 skipping in SMN (see esp. the abstract and introduction on p. 6307, discussion on pages 6310-6311).

Lim et al (J. Biol. Chem., Vol. 276, No. 48, pages 45,476-45,483, 2001, see IDS document No. 61, filed 12-30-05) teach the single nucleotide mutation in the splice site of the SMN gene which leads to the disruption of an exonic splicing enhancer and reduces the strength of the 3'-splice site of exon 7, reduces intron 6 removal, and increases the efficiency of competing exon 7 skipping pathway, which results in progression of spinal muscular atrophy. Lim also teaches enhanced stability, target binding and cellular uptake of oligonucleotides comprising 2'-O-methyl and phosphorothioate internucleotide modifications (see the abstract, introduction on pages 45,476-45,477; methods on page 45,478; fig. 2 on p. 45,479; discussion on pages 45,480, and 45,482-45,483).

It would have been obvious to design nucleic acid molecules comprising a first domain which forms a specific binding pair with a target sequence of SMN that is within 100 nucleotides of the defective RNA splicing site taught previously by Lorson and Lim, and which nucleic acid molecules further comprise a second specific binding pair with an RNA splicing factor appropriate for recruiting the relevant RNA splicing factors, enhancing exonic incorporation, and for recruiting

splicing factors to the target SMN RNA for treating spinal muscular atrophy (SMA) because the mutation linking this disease with incorrect or aberrant splicing was well known in the art at the time the instant invention was made. Furthermore, it would have required routine experimentation to design nucleic acid molecules targeting the mutation site and relying on the methods taught previously by Mitchell and Mitchell. One of ordinary skill in the art would have had a reasonable expectation of success for correcting the exon skipping phenomenon associated with SMA because the single point mutation causing this exon skipping was well known in the art, and the design of nucleic acid molecules for targeting and correcting this mutation were also well known in the art, relying on the teachings of Mitchell and Mitchell, whereby administration of pre-trans-splicing molecules designed to interact with the well known target precursor messenger RNA molecule of SMN would reasonably be expected to lead to trans-splicing to correct the mutated splice site. One of ordinary skill in the art would have been motivated to correct this genetic defect because the relationship between exon skipping and SMA disease severity had been well documented the prior art, and the means of generating pre-trans-splicing molecules to trans-splice the target pre-mRNA were also well known in the art to provide gene therapy approaches for correcting splicing disorders for known mutations.

One of ordinary skill in the art would also have been motivated to incorporate 2'-O-methyl and/or phosphorothioate internucleotide modifications into nucleic acid molecules for target cell delivery and uptake because these

modifications were well known in the art to enhance nucleic acid stability from nuclease degradations, as well as enhancing target cell uptake and target binding, as taught previously by many in the field, including Lim et al.

For these reasons, the instant invention would have been obvious to one of ordinary skill at the time the instant invention was made.

Claim Objections

Claim 68 is objected to because of the following informalities: in line 2 of claim 68, "phosphothiorate" appears to be a misspelling of phosphorothioate. Appropriate correction is required.

Allowable Subject Matter

Seq ID No. 16 (recited in claim 70) appears free of the prior art searched and of record.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE CO PIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
11-13-08

/Jane Zara/
Primary Examiner, Art Unit 1635